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14. ABSTRACT

. A clearly defined biological mechanism for the chronic illness reported by Gulf War (GW) veterans has remained elusive. Nevertheless, recently defined brain-immune system relationships point to a possible role for neuroinflammation as an underlying feature of Gulf War illness (GWI). Glia are no longer viewed simply as support cells of the brain. They play active roles in neural function and repair (astrocytes) and serve as neuro-immune signaling cells (microglia). Glial cells that make myelin sheaths (oligodendrocytes), are considered the white matter (WM) of the brain. WM allows for fast transmission of information across neuronal synapses and altered white matter pathways can result in cognitive deficits. The recent studies showing lower white matter volumes in GW veterans exposed to pesticides and low-dose sarin, suggest that glial cells may indeed have an important role in the development and continued maintenance of health problems afflicting GW veterans. This consortium development grant provided funding to plan for a full consortium grant submission that was submitted by leading experts in GWI and neuroinflammation to work collaboratively in order to assess the potential role of these pathobiological mechanisms in GWI. This consortium grant was submitted and was recently recommended for funding to continue these research consortium plans and to test these hypotheses of GWI.

15. SUBJECT TERMS- Gulf War Illness, consortium, CNS, innate immunity, neuroimaging, cognitive deficits, pesticides, sarin

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Table of Contents

INTRODUCTION

The Institute of Medicine (IOM) recently released the eighth volume of the Gulf War and Health report. In its conclusions and recommendations, the IOM recommended that future research should, "explore the biology of Gulf War Illness (GWI) in the context of identifying targets for therapies" (Institute of Medicine, 2010). The report further recommended that the goals of these studies include determining whether inflammation is associated with GWI, identifying genetic variation in genes that respond to environmental toxicants, improving the understanding of the basic symptom complex of GWI, enhancing understanding of the objective correlates of GWI, validating reported biomarkers of GWI, and focusing efforts on clinical treatment trials informed by the best biological data related to the cause of GWI. The Research Advisory Committee (RAC) on Gulf War Veterans Illnesses also recommended that neuroinflammatory processes and genomic technologies should be a primary target for Gulf War Illness research (RAC-GWVI, 2008).

It is with these recommendations in mind that the current consortium development grant, which builds upon the prior work of both seasoned GWI researchers and relevant subject matter experts, was designed. It is essential to combine forces and resources in order to identify the pathobiological mechanisms of GWI that will translate into focused and effective treatments. With the 20-year anniversary of the Gulf War now past, the most expedient way to elucidate the pathobiological consequences of GWI is by assembling these uniquely knowledgeable individual researchers into a collaborative research team. This multi-institutional collaboration of highly qualified GWI researchers from public universities, federal agencies, and the private sector, provide an unprecedented opportunity to more fully elucidate the underlying pathobiology of Gulf War illness in one integrated model that once proven, will lead to focused treatment trials that can be quickly implemented.

Specifically, this 1-year consortium development grant explored and built upon important recent advancements regarding the role of glia in chronic pain processing (Watkins et al., 2007; Watkins et al., 2009), axonal transport deficits in cognitive functioning difficulties (Falkinar & Baas, 2009; Middlemore-Risher et al., 2010; Terry et al., 2007; Grigorian et al., 2008) and mitochondrial damage with chronic fatigue-like illness (DiFillipo et al., 2010; Zhang et al., 2010); three of the most prominent symptoms of Gulf War illness (Figure 1). In this model, neurotoxicant exposures from the Gulf War including pesticides (organophosphates, OP), anti-nerve gas pills (pyridostigmine bromide, PB) and low-level nerve gas (sarin/cyclosarin) could have affected three types of glia: microglia, astrocytes and oligodendrocytes, causing glial priming and a chronic activation loop in some central nervous system (CNS) systems (Watkins et al., 2007; Watkins et al., 2009; Fields, 2009). Recent advances in test methodologies for genetic polymorphisms and glial markers of neuroinflammation now make testing this theory possible (Watkins et al., 2009; Fields, 2009; Liu et al., 2009). The ultimate goal of this proposed consortium will be to identify validated biomarkers of illness that can be easily translated into future clinical treatment trials. This goal will be accomplished by assembling subject matter experts in neuronal cell cultures, animal models and clinical studies in order to incorporate a truly translational approach that will provide a *bench-to-bedside-to-bench strategy*. In this way, the animal and cell culture research will initially inform the clinical component and then later be used to validate the clinical findings. From these pathobiological findings, specific treatment options could be chosen based on plausible and proven biological mechanisms. A major strength of this consortium development study therefore lies in the assembling of an expert group of bench scientists and

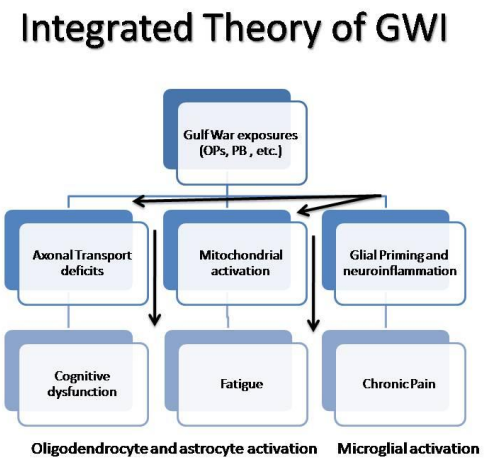


Figure 1. Integrated Gulf War Illness Model

clinicians working collaboratively in an integrated research program that will not only validate initial results in multiple modalities but also improve the speed with which specific treatment foci are identified. Given the new focus on identifying pharmaceuticals specifically focused on glial functions Watkins et al., 2007; Fields, 2009), establishing how this proposed glial mechanism is altered in veterans with GWI is of paramount importance. In order to specifically address the research gaps outlined by the IOM and the RAC reports, this team will characterize disease symptoms and validate and improve diagnostic markers based on collective prior clinical (Sullivan et al., 2003; Toomey et al., 2009; Whistler et al., 2009 and preclinical studies (Falkinar & Baas, 2009; Middlemore-Risher et al., 2010; Terry et al., 2007; Grigoryan et al., 2008; DiFilippo et al., 2010, Zhang et al., 2010) with the ultimate goal of identifying targeted and effective treatments. This multi-institutional collaboration includes both seasoned GW researchers (with large well-established GW veteran cohorts) and experts in neuroinflammation, neuroimaging, neuroanatomy, genetics, cell biology and immunology working together to gain insights from each other and advance the field of GWI research. This research has gone beyond the stage of individual field advancements into multisystem theories that require true multidisciplinary teams to effectively elucidate its pathobiology. This consortium will examine all of the facets of GWI in an integrated and highly testable hypothesis that will be further elaborated on in the grant proposal recently submitted by the GWIC consortium members and recommended for funding by CDMRP.

BODY

The approved statement of work for the entire study period is below:

STATEMENT OF WORK

Brain-Immune Interactions as the Basis of Gulf War Illness: Consortium Development

Task 1. Develop Plan for Gulf War Illness Consortium (GWIC) Studies (Months 1-12)
A. Conduct two in-person meetings at BUSPH of all consortium collaborators to plan for full GWIC consortium research studies by including scientific presentations and discussions (Months 1-12; BUSPH, Sullivan, and GWIC Collaborators)
B. Conduct monthly teleconference/videoconference meetings to further plan for full consortium studies and consortium structure (Months 1-12; BUSPH, Sullivan, and GWIC Collaborators)
Task 2. Develop GWIC Study Aims and Objectives for Clinical and Preclinical Consortium Cores (Months 3-12)
A. Identify specific study aims for clinical and preclinical cores that will both validate and inform each other in order to advance the study of pathobiological mechanisms of Gulf War Illness (Months 3-7; BUSPH, Sullivan, and Collaborators)
B. Identify key collaborations between preclinical and clinical cores to maximize data and resources (Months 3-7; BUSPH, Sullivan, and Collaborators)
C. Identify specific Research Sites for collaborative studies (Months 3-7; BUSPH, Sullivan, and Collaborators)
Task 3. Develop Quality Control and Oversight Plan for Administrative Core (Months 3-12)
A. Quality control measures will be devised by Administrative Core Members and among potential Research Site collaborators to ensure robust data quality between sites (Months 7-12; BUSPH, Sullivan, and Collaborators)
B. External Advisory Committee will be planned (Months 10-12; BUSPH, Sullivan, and Collaborators)
Task 4. Intellectual Property Plan (Months 1-12)
A. Identify any potential intellectual property or materials that should be discussed among consortium collaborators (Months 1-5; BUSPH, Sullivan, and GWIC Collaborators)
B. Devise an intellectual property plan across all institutions and individuals (Months 6-12; BUSPH, Sullivan, and GWIC Collaborators)
Task 5. Report Writing (Months 10-12)
A. Finalize GWIC consortium plan regarding specific study aims and scientific collaborators (Months 7-12; BUSPH, Sullivan, and GWIC Collaborators)
B. Write brief final planning summary report documenting GWIC plans for Administrative, Preclinical and Clinical consortium Cores and identify Research Sites for planned studies (Month 12; BUSPH, Sullivan, and GWIC Collaborators)
C. Prepare GWIC consortium grant draft for submission (Month 12; BUSPH, Sullivan, and GWIC Collaborators)

Task 1a. Conduct two in-person meetings at BUSPH of all consortium collaborators to plan for full GWIC consortium research studies by including scientific presentations and discussions.

An in-person consortium development kick-off meeting was held at BUSPH in Boston on June 7, 2011 where the monthly web conference meetings were planned for the year and where scientific presentations were presented by Dr. Kimberly Sullivan and Ms. Christine Chaisson from BUSPH, Dr. Janet Coller from University of Adelaide and Dr. John Forsayeth from Rio Pharmaceuticals. Discussions were started regarding neuropsychological and neurotoxicant effects in GW veterans, potential immune-genetic studies and advanced neuroimaging PET ligands as potential studies for the GWIC consortium grant proposal. Monthly web meetings were then conducted (see below).

A final in-person consortium development meeting was held at BUSPH on May 15, 2012 where the GWIC grant plans were finalized for the June 2012 grant submission. At this meeting, Dr. Sullivan presented the current overall specific aims and hypothesis and agreed upon consortium structure to the consortium members for discussion. The GWIC investigators then presented their research plans for their respective studies to the consortium members for discussion and finalizing of their plans for grant submission.

Task 1b. Conduct monthly teleconference/videoconference meetings to further plan for full consortium studies and consortium structure.

Monthly web conference meetings were successfully held at agreed upon times with investigators from ten study sites including international collaborators in Australia. Table 2 below describes the meeting schedules and topics of each planning meeting. Adobe ConnectPro was used for web meetings and was found to work very well for meetings with multiple sites, locations and time zones. This software was used during the rest of the funding period and will continue to be used for the full consortium study.

Table 2. GWIC Meeting Summary

Date	Type of Meeting	Discussion item	Presenter
June 7th, 2011	In-person	1. Introduction to GWIC 2. RIO – PET ligands 3. Addiction Genetics – Polymorphisms and Saliva Collection 4. BU Data Coordinating Center (DCC)	Kimberly Sullivan John Forsayeth Janet Coller Christine Chaisson
July 6th, 2011	Webinar	1. GWIC updates 2. Neuronal Inflammation, Glial Activation, Neurotoxicity	Kimberly Sullivan James O'Callaghan
August 3rd, 2011	Webinar	1. GWIC updates 2. Axonal Transport 3. Nanostring Technology	Kimberly Sullivan Mark Black and Peter Baas Nancy Klimas
September 7th, 2011	Webinar	1. GWIC updates 2. The Innate Immune System 3. Glia as the Bad Guys 4. GWI Research – Who Do We Study	Kimberly Sullivan Steven Maier Linda Watkins Lea Steele
October 5th, 2011	Webinar	1. GWIC Updates 2. MRI Techniques to Study GW Veterans 3. GWI – Neuropsychological Assessment 4. Clinical Core Discussion	Kimberly Sullivan Ronald Killiany Maxine Krengel Kimberly Sullivan
November 2nd, 2011	Webinar	1. Discussion of Individual Projects Planned	Kimberly Sullivan and whole group
December 7th, 2011	Webinar	1. GWIC Updates 2. Continued Discussion of Projects	Kimberly Sullivan Group
January 4th, 2012	Webinar	1. Project Planning 2. BU DCC 3. Group Discussion – Grant Planning	Kimberly Sullivan Christine Chaisson Group
February 8th, 2012	Webinar	1. Grant Project Planning 2. Intellectual Property Plans	Kimberly Sullivan Michael Pratt
March 7th, 2012	Webinar	1. Grant Project Planning 2. Pilot Findings – Rat and mouse models	Kimberly Sullivan Jim O'Callaghan
May 15th, 2012	In-person	1. Grant Project Planning 2. Individual Project Discussions 3. Group Discussion	Kimberly Sullivan PI's for each study Group

Task 2. Develop GWIC Study Aims and Objectives for Clinical and Preclinical Consortium Cores.

The central hypothesis for the pathobiological mechanisms of GWI in this consortium includes chronic neuroinflammation as a result of initial glial *activation* and then *priming* of glial responses that cause stronger and longer responses that do not shut off the chemical cascade of proinflammatory cytokines and chemokines that cross-talk between the immune system and the brain. This could result in a lasting multisystem illness affecting many body systems, as seen in GWI. Advanced neuroimaging techniques using high resolution MRI, DTI, fMRI and newly developed PET imaging agents that can assess glial activation *in-vivo* (and the neurochemical systems that they affect), and genetic polymorphism and proteomic studies of TLR4 and glial activation products in blood and cerebrospinal fluid (CSF) to assess for individual susceptibilities, will be assessed in an interdisciplinary way in this multidisciplinary consortium. Clinical studies will also include neuropsychological assessments to assess structure (neuroimaging) and functional (cognition) relationships.

Neurotoxicant exposures from the Gulf War including organophosphate (OP) and other pesticides, anti-nerve gas pills (PB) and low-level nerve gas (sarin/cyclosarin) could have affected three types of glia: microglia, astrocytes and oligodendrocytes, by:

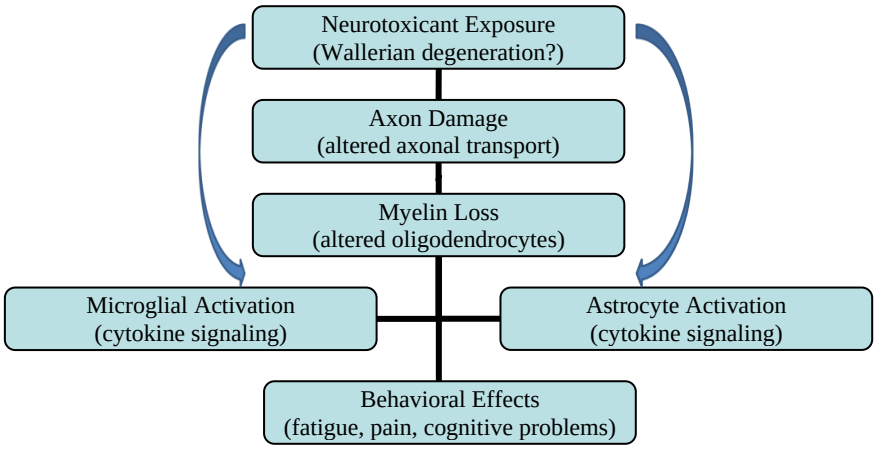
1) directly causing glial priming and a chronic activation loop perpetuated by physical stressors and the resultant release of proinflammatory cytokines in some CNS mechanisms (Spradling et al., 2011).

2) indirectly through glial activation as a result of myelin and cellular debris acting as endogenous danger signals for TLR chronic signaling of cytokines (Milligan et al., 2009; Rivest, 2009).

This provides two highly testable hypotheses for the chronic symptoms of GWI mechanisms that will be assessed in the planned full GWI consortium (GWIC) studies. These two hypotheses for GWI may not be

mutually exclusive and once tested, may be shown to act in synergistic ways if both are shown to be relevant to GW-related exposures and symptoms (Figure 2).

Figure 2. Schematic Representation of Hypothesized GWI Mechanisms



A recent review has further documented OP-induced inflammatory mechanisms in both acute and chronic low-level OP exposures (including sarin) suggesting that neuroinflammatory markers as a result of oxidative stress and glial activation may serve as surrogate biomarkers of OP exposures (Banks & Lein, 2012). This could cause an imbalance of neuron-glia communications and lead to axonal and mitochondrial damage and/or altered myelination (Schmitz, 2008). Specifically, the negative impact on axonal transport leads to neurodegeneration, and the resulting degeneration products then enhance and sustain the proinflammatory response of the microglia, creating an iterative cycle of inflammation, impaired axonal transport and degeneration that underlies the impaired brain-immune functioning in veterans suffering from GWI. Exposure to Gulf War neurotoxicants can depress axonal transport through both direct effects on neurons and indirect effects mediated by proinflammatory factors from microglia, and this can lead to low levels of neurodegeneration. These pathobiological events could then lead to the neurological and immune processes that manifest as chronic illness and are symptomatically

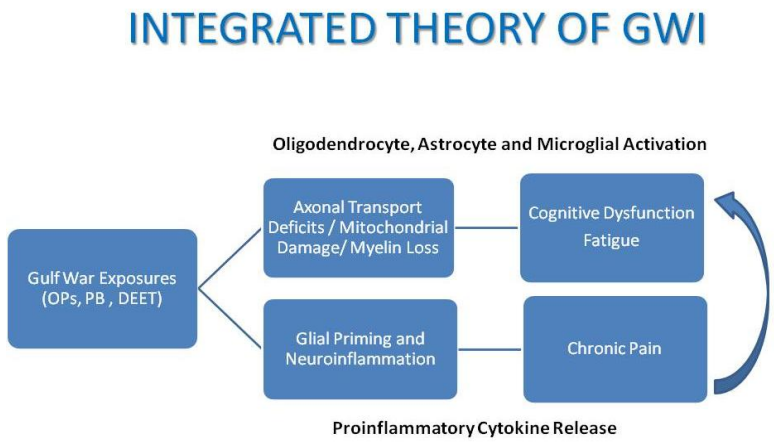


Figure 3. Integrated Theory of GWI

characterized by persistent pain, cognitive dysfunction, and fatigue—the hallmark symptoms of GWI (Figure 3).

More specifically, (1) the role of glia and resultant release of proinflammatory cytokines can lead to chronic pain and diminished cognitive processing, (2) axonal transport deficits and myelin alterations can lead to cognitive functioning difficulties, and (3) mitochondrial damage can lead to chronic fatigue-like illness. As support for this model, the current Boston investigators have found that GW veterans with known OP exposures showed significantly worse performance on information processing speed of sustained and selective attention, visual memory, and altered mood compared with less exposed GW veterans (Krengel, 2010; Sullivan, 2009), and GW veterans with PB exposure showed significantly lower performance on a task assessing executive system functioning (Sullivan et al., 2003). In addition, this team of researchers found that symptomatic treatment-seeking GWVs showed worse performance on measures of attention, memory, visuospatial functioning, and mood alterations (Sullivan et al., 2003). Correspondingly, two recent MRI studies have shown lower white matter volumes in sarin-exposed GW veterans (Chao et al., 2011; Heaton et al., 2007). Neuronal and myelin breakdown products can take years to be cleared from the CNS due to Wallerian degeneration and die-back mechanisms may cause microglial activation and corresponding innate immune system activation as the microglia are considered the immune sentinels of the CNS (Milligan et al., 2009; Rivest, 2009; Vargas et al., 2007).

Behaviorally, the symptoms of fatigue, memory loss, and attentional deficits reported by GW veterans are similar to those seen in patients with diseases of the white matter that are also mediated by brain-immune interactions and cytokine signaling such as multiple sclerosis (Dworzanska, 2009; Pantoni, 2009) and chronic fatigue syndrome (CFS) (Baraniuk, 2005; Brimacombe et al., 2002; Lange et al., 1999; Zhang et al., 1999). Increased sensitivity to pain has also been related to proinflammatory cytokine signaling in the CNS in fibromyalgia and CFS and is often referred to as central sensitization (Arnett, 2012). Recent studies of GW veterans with chronic pain have also reported central sensitization of pain on functional MRI imaging

(Gopinath et al., 2012). When considered in relation to reported increased rates of proinflammatory cytokines in blood samples from GW veterans with CFS when compared with either healthy GW veterans or civilians with CFS, the results suggest that neuron-glial and innate immune alterations appear to be associated with GWI and should be further studied as potential biomarkers of illness (Brimacombe et al., 2002; Zhang et al., 1999).

Recent advances in test methodologies for glial markers of neuroinflammation and genetic polymorphisms now make testing these inter-relationships possible. The ultimate goal of this proposed consortium will be to identify the pathobiological mechanisms and validated biomarkers of GWI that can be easily translated into targeted future clinical treatment trials.

Improved understanding of the role of glial activation in chronic pain states has given rise to rapidly expanding efforts to identify pharmaceuticals that specifically focus on glial functions. The growing availability of treatments of this type gives particular urgency to our efforts to determine the extent to which glial activation and central cytokine activation explain the symptoms of GWI. In order to specifically address the research gaps outlined by the IOM and the RAC reports with regard to biomarker identification and pathobiology of GWI, this team will be characterizing disease symptoms and validating and improving pathobiological markers based on collective prior clinical and preclinical studies and leveraging longitudinal cohorts and stored blood samples with the ultimate goal of identifying targeted and effective treatments for GWI. This multi-institutional collaboration will include experts in GWI research, toxicology, neuroinflammation, neuroimaging, neuroanatomy, immune genetics, cell biology and immunology working together to gain insights from each other and advance the field of GWI research in the most expedient manner. This proposal will examine diverse facets of GWI in an integrated and highly testable hypothesis that involves brain-immune interactions and signaling pathways that, based on previous findings, have the potential to explain the fundamental mechanisms responsible for the persistent illness affecting Gulf War veterans.

Task 2a. Identify specific study aims for clinical and preclinical cores in order to advance the study of pathobiological mechanisms of Gulf War Illness.

During this 1-year planning period, regular monthly web meetings were held to plan for the overall GWI consortium (GWIC) structure including finalizing the study aims and objectives for the clinical and preclinical consortium cores and the administrative core structure.

Objective/Hypothesis: The goal of the full GWIC consortium is to study the pathobiological mechanisms of GWI and to identify targeted treatment strategies. We have assembled a team of seasoned GWI researchers and scientific experts in all the proposed areas of research, both preclinical and clinical. The full consortium will allow for implementation of multidisciplinary collaborations that will target suspected brain-immune signaling alterations in GWI. The GWIC consortium central hypothesis identifies chronic neuroinflammation as an end result of initial glial *activation* and subsequent *priming* of glial responses that cause a chronic activation loop of stronger and longer proinflammatory effects between the immune system and the brain.

Specific Study Hypotheses:

1. Axonal transport, microtubule and mitochondrial transport deficits will occur in rodent and cell models for an extended period after animals are exposed to neurotoxicants or cytokines similar to those experienced by military personnel in the Gulf War.

2. Persistent histological and neurochemical changes indicative of chronic glial activation and myelin alterations will occur in rodent models for an extended period after exposure to neurotoxicants similar to those experienced by military personnel in the Gulf War.

3. "Sickness behavior"-type changes in pain sensitivity, learning, and memory will occur in rodent models for an extended period after exposure to neurotoxicants similar to those experienced by military personnel in the GW.

4. Immune, neurobehavioral, and genetic measures associated with GWI in veterans will parallel immune, neurobehavioral, and immune genetic turnover rate differences associated with neurotoxicant exposures in animal models.

5. GWI is associated with neuroimaging measures indicative of reduced white matter volume and integrity and central nervous system inflammation in GW veterans.

6. GWI is associated with peripheral blood measures (circulating cytokines, mRNA) indicative of a chronic upregulated inflammatory state in GW veterans.

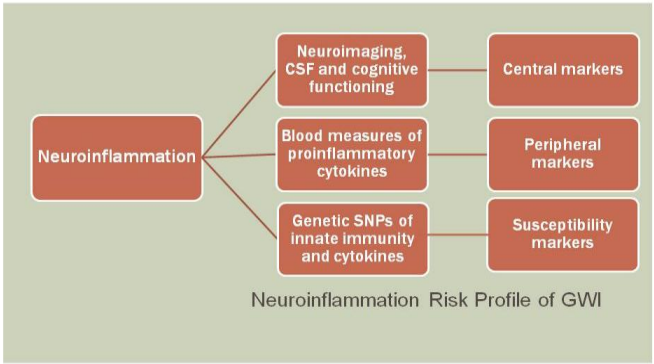
7. Significant correlations exist among a) neuroimaging measures of white matter volume, integrity and neuroinflammation, b) peripheral measures of innate immune activation, and c) cognitive decrements identified on neuropsychological testing in GWI and with reported health symptoms including fatigue and pain in GW veterans.

8. GWI is associated with genetic susceptibility markers associated with innate immune functions in GW veterans.

9. Viable treatment avenues for GWI will be found by targeting identified chronic neuroinflammatory activation and validating them in preclinical models to inform the best choice of clinical trial models.

Overall Aims: The overall aims of this integrated multidisciplinary consortium scientific focus will be:

Figure 15. Neuroinflammation Risk Profile of GWI



(1) To identify validated markers of GW illness by using state of the art neuroimaging, behavioral, genetic and blood markers of neuroinflammatory activation in both clinical and preclinical models that will elucidate targeted and validated treatment strategies (2) To create a Neuroinflammation Risk Profile for GWI (3) To identify viable

mechanistic treatments based on identified pathophysiological pathways of GWI that have been validated in preclinical treatment models.

Specific Aims:

Aim 1. To assess axonal transport functioning and myelin integrity in cell studies and rodent GWI neuroinflammatory models.

Aim 2. To delineate the relative contributions of astrocytes and microglia in rodent GWI neuroinflammatory models to identify potential cellular and molecular markers of GWI and lead to candidate "drugable" targets.

Aim 3. To compare behavioral testing of learning and memory and enhanced pain, in rodent GWI neuroinflammatory models.

Aim 4. To compare central and peripheral inflammatory measures in brain tissue and blood from 60 rodent GWI neuroinflammatory models.

Aim 5. To compare diverse brain and innate immune measures in well-characterized samples of 200 veterans with GWI and 100 healthy GW veterans at clinical study sites in Boston, Miami, and Central Texas by comparing neuroimaging, cognitive assessments and blood measures and correlating these markers.

Aim 6. To compare immune genetic and neuroendocrine measures in well-characterized samples of 200 veterans with GWI and 100 healthy GW veterans at clinical study sites in Boston, Miami, and Central Texas by comparing saliva samples of cortisol measurements and genetic polymorphisms of innate immune functions.

Aim 7. To compare central and peripheral inflammatory measures in cerebrospinal fluid and blood samples from 25 veterans with GWI and 25 healthy GW veteran controls.

Aim 8. To compare specific neuron-glia signaling mechanisms in advanced and specialized neuroimaging measures (positron emission tomography, PET) in 30 veterans with GWI and 15 healthy controls.

Aim 9. To compare several relevant preclinical treatments for GWI including inflammatory glial activation modulators, antioxidants, and neuroprotective peptides in cell and animal models.

Task 2b. Identify key collaborations between preclinical and clinical cores to maximize data and resources.

The overall research focus for this consortium is to identify whether chronic neuroinflammation as evidenced by glial activation and signaling of proinflammatory cytokines, chemokines and excitatory neurotransmitters is associated with the varied symptoms (cognitive dysfunction, fatigue, pain) of GWI. To accomplish this research focus, individual studies will be conducted that will assess whether GW-relevant exposures and physical stressors have either caused damage to the axon and/or myelin sheath in the brain and then indirectly caused chronic glial activation loops, or directly caused chronic glial activation loops (microglia, astrocytes, oligodendrocytes) and cross-talk between the brain and the immune system perpetuated by physical stressors resulting in the release proinflammatory cytokines, chemokines and excitatory neurotransmitters and the primary symptoms of GWI (i.e. cognitive problems, fatigue, chronic pain). The central hypotheses for the GWIC will study chronic neuroinflammation as a result of initial environmental exposures during the GW either directly or indirectly causing a chronic glial activation loop of the innate immune system (TLR4) resulting in chronic functional illness and affecting multiple body systems. The 10 planned studies include 5 preclinical and 5 clinical studies that are designed to assess separate and combined aspects of this main theory of GWI. For example, preclinical studies will directly assess axonal and myelin integrity after GW-relevant neurotoxicant exposures in animal and cell studies to assess whether these chemicals cause direct damage to these neural systems that will correspond to clinical brain imaging studies. Other studies are designed to assess the direct impact of these chemicals and physiological stressors on proinflammatory cytokine signaling and the development of chronic neuroinflammation and sickness response behaviors in animal models to mimic the human GWI condition. Corresponding clinical studies will be designed to assess for markers of central and peripheral measures of neuroinflammation (proinflammatory cytokines, chemokines, glutamate) and correlations of these markers with behavioral measures relevant to GWI (cognitive decrements, fatigue, chronic pain). These studies will include advanced structural and functional neuroimaging measures, cognitive assessments, blood markers, cerebrospinal fluid markers, and saliva markers of neuroinflammatory indicators (cytokines, chemokines), genetic susceptibility (genetic polymorphisms) and neuron-glial signaling

alterations of homeostatic mechanisms (glutamate) that could result in chronic illness. Identified proinflammatory cytokine markers of GWI will be further validated in other stored specimen samples from a prior large study of GW veterans. Positive markers of neuroinflammation in GWI will then be combined to assess whether a stronger additive 'neuroinflammation risk profile of GWI' can be devised by combining identified markers in GWI.

Preclinical treatments will also be planned for the GWIC in order to identify potential viable therapies that could then be turned into separate treatment trial grant proposals and for identifying which models are not shown effective before the large cost and time of trying them in human trials. Specific preclinical studies currently planned include beta-adrenergic agonist propranolol and the flavonoid antioxidant luteolin will be used to decrease microglial activation, oxidative stress and neuroinflammation (see background section) and davunetide (NAP), a potent neuroprotective peptide that interacts with brain tubulin and protects neurons from a variety of insults to the microtubule system, including oxidative stress, deficiencies in microtubule-associated proteins, and metal intoxication, in clinical and preclinical models (Divinski et al., 2006; Gozes et al., 2011; Gozes 2011; Zemylak, 2009). Other treatments of specific glial modulators will be planned after initial study results are obtained and identification of specific altered glial or immune pathways are identified. Some of the reserve exploratory funds will be planned for this transitional use. Several GWIC investigators have extensive experience with pharmacological development of glial modulation therapies (Drs. Watkins, Maier, O'Callaghan, Hutchinson, Coller) and others are currently funded for treatment trials for GWI or are providing clinical therapies for ill GW veterans (Drs. Sullivan, Krengel, Klimas) and will be instrumental in assisting with the transition from preclinical treatments to identifying the most viable agents for application for clinical trials in GW veterans. This will be a strategic plan of the GWIC translation goals.

Overview of Preclinical Studies - The preclinical studies will be conducted in order to test the two main hypotheses above regarding the potential pathobiological mechanisms of GWI in cell and animal models. To accomplish this research focus, individual studies will be conducted that will assess whether GW-relevant

exposures and physical stressors have either caused damage to the axon and/or myelin sheath in the brain and then indirectly caused chronic glial activation loops, or directly caused chronic glial activation loops (microglia, astrocytes, oligodendrocytes) and cross-talk between the brain and the immune system perpetuated by physical stressors resulting in the release proinflammatory cytokines, chemokines and excitatory neurotransmitters and the primary symptoms of GWI (or sickness response behaviors in these animal models). Determining which and if both hypothesized effects are present in preclinical models will help to determine which specific treatment avenues should be chosen for translation to the clinical setting. Preclinical animal and tissue studies will be coordinated to maximize data sharing and reduce redundancy by all investigators using a developed and validated model of GW-exposures that was developed by Dr. Jim O'Callaghan from CDC-NIOSH that he has established produces neuroinflammatory activation in mouse and now rat models. Dr. O'Callaghan will provide dosed animals to other animal researchers for their planned studies to maximize multidisciplinary collaborations and to reduce duplication of resources across the consortium. Studies will be conducted by Dr. Douglas Fields from NIH who has extensive experience in neuron-glia signaling, Drs. Linda Watkins and Steven Maier from University of Denver who have extensive experience in glial activation in pain and cognitive/behavioral alterations, Dr. Peter Baas from Drexel University and Dr. Mark Black from Temple University who are axonal transport experts and Dr. Nancy Klimas from the Miami VA who has extensive experience with gene expression proteins and immunological consequences. These five animal and tissue studies will both inform and validate the clinical studies and provide direction for future clinical treatment trials based on identified pathobiological markers. Individual animal and tissue studies are planned to assess the overall hypotheses of the consortium by investigating specific pathobiological mechanisms of chronic glial activation thought to be associated with GW-relevant exposures.

Overview of Clinical Studies - The central objective of the Clinical Studies Core of the consortium is to provide an extensive evaluation of brain and immune function in 1991 Gulf War veterans to identify individual measures, and combinations of measures, that significantly distinguish veterans with GWI from

healthy controls. Studies of Gulf War veterans will be conducted at three clinical study sites that utilize identical methods to characterize GWI and controls in three distinct cohorts—Boston, Miami, and Central Texas—in order to identify differences that are consistent between sites. In addition to direct measures of brain structures, brain function, plasma immune parameters, and salivary cortisol, the study will collect samples to assess genetic variability in relation to immune function. Additional studies in individual cohorts will provide longitudinal assessment of key brain-immune measures (Texas cohort), evaluation of immune measures in cerebrospinal fluid (CSF) (Boston cohort), and pilot testing of an innovative imaging method for visualizing neuroinflammaiton in the brain (Boston cohort). The ultimate goal of the clinical studies is to provide a detailed understanding of the pathobiology of GWI that can be used to develop targeted treatment strategies and establish valid diagnostic markers.

Table 2. Correlation of Evaluation Measures To Be Assessed in Human and Animal Studies

EvaluationMeasures	Clinical studies	Preclinical studies
Brain tissue, including white matter integrity and inflammation indicators	Neuroimaging of structural integrity and volumes, DTI, fMRI, relaxometry, PET imaging of glial activation	Stains GFAP, Fluoro-jade-B, isolectin B4, phosphorylated JNK, myelin integrity studies and axonal transport integrity studies
Cognitive/behavioral assessments	Cognitive assessment and health symptom report of fatigue, chronic pain and other relevant measures.	Behavioral assessment of learning and memory and pain measures in rats
Central nervous system immune signaling	Cerebrospinal fluid levels of IL-1alpha, IL-1beta, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p70, IL-13, IL-15, IL-17, IL-21, IL-23, IL-27, IFN gamma, TNF alpha, LT alpha, TNFRI,TNFRII, sIL-1RA, sIL-6R, sCD-26 (Aka DPP4 or DPPIV), CRP, and MIP-1alpha, MCP-1, LIF, BDNF, gluatmate	Brain tissue levels of IL-1alpha, IL-1beta, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p70, IL-13, IL-15, IL-17, IL-21, IL-23, IL-27, IFN gamma, TNF alpha, LT alpha, TNFRI,TNFRII, sIL-1RA, sIL-6R, sCD-26 (Aka DPP4 or DPPIV), CRP, and MIP-1alpha, MCP-1, LIF, BDNF, glutamate
Blood immune signaling	IL-1alpha, IL-1beta, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p70, IL-13, IL-15, IL-17, IL-21, IL-23, IL-27, IFN gamma, TNF alpha, LT alpha, TNFRI,TNFRII, sIL-1RA, sIL-6R, sCD-26 (Aka DPP4 or DPPIV), CRP, and MIP-1alpha, MCP-1, LIF, BDNF	IL-1alpha, IL-1beta, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p70, IL-13, IL-15, IL-17, IL-21, IL-23, IL-27, IFN gamma, TNF alpha, LT alpha, TNFRI,TNFRII, sIL-1RA, sIL-6R, sCD-26 (Aka DPP4 or DPPIV), CRP, and MIP-1alpha, MCP-1, LIF, BDNF

Task 2c. Identify specific Research Sites for collaborative studies.

The Brain-Immune interactions as the basis of GWI consortium (GWIC) structure was planned to provide maximum centralized support of data management and statistical support for the exceptional preclinical and clinical GWIC core laboratories and individual research sites (Figure 5). The GWIC research cores will include a preclinical and a clinical core and a laboratory core. Working groups by scientific specialty or for support services (data management, statistics) will also be planned to ensure adequate communication and support for the GWIC members. As the overall research focus for the GWIC is to identify whether chronic neuroinflammation as evidenced by glial activation and signaling of proinflammatory cytokines, chemokines and excitatory neurotransmitters is associated with the varied symptoms (cognitive dysfunction, fatigue and pain) of GWI, the preclinical and clinical cores will be designed to assess different aspects of this hypothesis and to inform and assist each other in understanding the pathobiology of GWI. In total, 9 research sites will be included in this consortium including Boston University, Nova Southeastern University/Miami VA, Baylor University, University of Colorado, University of Adelaide, CDC/NIOSH, NIH, Drexel University and Temple University. The specific research cores and planned studies in each research site are described below.

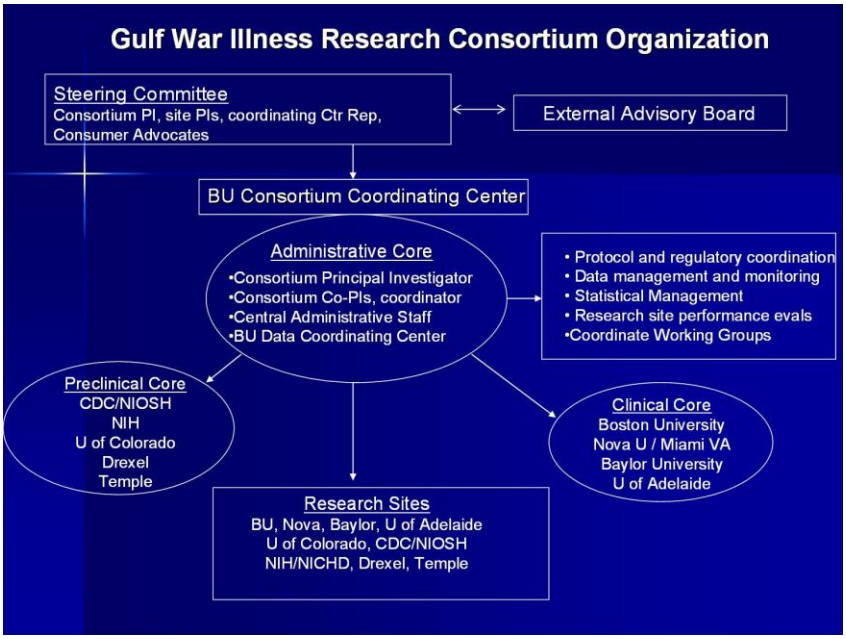


Figure 5. Gulf War Illness research consortium(GWIC) Structure

The Preclinical Research Core - will include very highly experienced and well-equipped laboratories that will study the cell and animal correlates of GW-relevant neurotoxicant models of GWI by using a model of

neurotoxicant exposures relevant to GWI designed by Dr. Jim O'Callaghan from CDC/NIOSH who is currently funded to study GW relevant neurotoxicant exposures and resultant neuroinflammatory effects. All preclinical core members will use Dr. O'Callaghan's validated mouse exposure model of GWI that involves exposure to PB, DEET and the sarin surrogate DFP in association with corticosterone to simulate stress over time and chronic glial activation effects. In addition, Dr. O'Callaghan has provided preliminary data for this exposure model in the rat now as well thus validating interspecies correlates of this GW-relevant model in animals. This is designed to assess chronic illness in GW veterans that has lasted for more than 20 years and has shown to be a valid model of GWI exposures in his initial mouse study funded by CDMRP. Therefore, Dr. O'Callaghan will be the core director for the preclinical core and will work with the other extremely talented core PIs including Drs. Linda Watkins and Steven Maier from the University of Colorado, Dr. Doug Fields from NIH and Dr. Peter Baas from Drexel University and Dr. Mark Black from Temple University. This will provide the foundation for Drs. Maier and Watkins planned studies of memory and pain studies in rats following Dr. O'Callaghan's dosing regimen and with cytokines to assess affects of neuroinflammation on memory and pain functioning. For this consortium, Dr. O'Callaghan will dose and prepare animals according to his dosing regimen and send them to the other research sites for analysis. Dr. Maier and Watkins' lab was the first to show that there are neural communication routes from the immune system to the brain, that peripheral inflammatory events induce neuroinflammation via these routes, that these neuroinflammatory events produce memory impairment, and that these neuroinflammatory events produce exaggerated pain and are therefore the experts to perform this research in a GW-relevant model. Drs. Baas and Black are experts in axonal transport (AXT) and have made important discoveries regarding AXT mechanisms and have worked collaboratively for many years. They will work to assess whether Dr. O'Callaghan's GW-relevant exposure model alters axonal transport mechanisms in cell and animal studies. Dr. Doug Fields will also plan to build upon his extensive work with neuron-glia communication and myelination to assess whether the GW-relevant exposure model developed by Dr. O'Callaghan alters myelination in animal models and cell culture studies as has been shown in GW veteran clinical samples and if these effects are directly related to GW-relevant exposures or resultant cytokine signaling from glial

activation. The preclinical core will be able to directly assess the two GWIC hypotheses of neuroinflammation in GWI (i.e. 1. neurotoxicants directly cause glial activation and neuroinflammatory signaling loops 2. neurotoxicants cause myelin and axonal transport damage that results in cellular and myelin debris 'damage' signals that cause chronic glial (microglia and/or astrocyte) activation loops and proinflammtion cytokine signaling).

The Clinical Research Core – will include GWI research and subject matter experts with established cohorts of GW veterans as study participants. The three clinical sites where subject recruitment will occur will be in Boston, Miami and Central Texas. The clinical research core includes Dr. Kimberly Sullivan from Boston University and her team of neuroimaging and neuropsychology experts, Dr. Nancy Klimas from Nova University and the Miami VA Medical Center who is a board certified immunologist and is currently funded to study immune and gene expression alterations in GW veterans and Dr. Lea Steele from Baylor University who is an epidemiologist and GWI expert who authored the Kansas GWI case criteria, one of the more widely used GWI case definitions. The clinical core will also include Drs. Janet Coller and Mark Hutchinson from the University of Adelaide who are experts in immune-genetics and will provide analysis of genetic polymorphisms thought to be related to increased rates of glial activation and neuroinflammation. The clinical research core members will all use the Kansas GWI criteria for determining cases and healthy controls for the planned clinical studies that will include neuroimaging, neuropsychological evaluations, blood analysis of immune parameters of inflammation and saliva analysis of immune genetic polymorphisms. Dr. Klimas will provide the laboratory core and will be the laboratory director for the clinical research group and bloods, saliva and cerebrospinal fluid that will be sent to Dr. Klimas for central analysis of these biological samples from the three clinical study sites at Boston University, Baylor University and the Miami VA. Additional saliva samples will be sent to Dr. Coller at the University of Adelaide for processing of genetic polymorphisms of innate immune and cytokines measures. Dr. Coller has successfully worked with other US investigators to analyze saliva samples for genetic analysis through standardized shipping and specimen preparation procedures.

Boston University Coordinating Center (BUCC) -The coordinating center for this consortium will be housed at the Boston University School of Public Health (BUSPH) and the *Principal Investigator* will be *Dr. Kimberly Sullivan*. The primary responsibilities and activities of the coordinating center will be to provide central planning and communication for the entire consortium. The in-person and web-based meeting platforms that were very successfully implemented in the GWIC developmental phase will continue to be utilized in the full consortium. The BUCC will also be a central place for data management, administrative and operational support for the GWIC and specific working groups will be devised for these purposes (see below). BUCC will also provide support for study coordination, study management and monitoring, regulatory coordination, intellectual property coordination and for developing standard operating procedures (SOPs) for the GWIC. The coordinating center will include key personnel with extensive experience with multisymptom illness research as well with multi-institutional collaborations. In addition to Dr. Sullivan, *Boston University Coordinating Center (BUCC) key personnel* will consist of Drs. Maxine Krengel, Rosemary Toomey, Ronald Killiany and Timothy Heeren and Boston University Data Coordinating Center (DCC) personnel including Christine Chaisson. All of these investigators have significant experience working with and coordinating large multi-site studies and will be ideal for the coordination of the GWIC. For example, they have been involved in large longitudinal cohort studies including The Ft. Devens Cohort studies and the Framingham Heart Study (Myers et al., 1996; Seshadri et al., 1997) (Drs. Sullivan, Krengel, Killiany and Heeren) as well as large multi-site national studies including VA Cooperative Study #458 National Health Survey of Gulf War Veterans and Their Families (Toomey et al., 2009; Toomey et al., 2007), the Vietnam Era Twin Study of Aging (Lyons et al., 2009) (Dr. Toomey), and the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Jack et al., 2008) (Dr. Killiany). Collectively, the proposed BUCC personnel have extensive experience coordinating large longitudinal and multi-site studies including responsibility for reducing inter-rater drift and ensuring data reliability and secure data practices and quality control measures (Drs. Toomey and Krengel). Dr. Toomey will direct the quality control aspects of the clinical studies in GWIC, Dr. Killiany will provide quality control and central processing for the neuroimaging data, Ms. Chaisson will provide data management and statistical support for the GWIC with the

assistance of Dr. Heeren. Full details of individual working groups within the BUCC and the administrate core are listed below.

Administrative Core – will be made up of the consortium PI Dr. Sullivan, consortium co-PIs, central administrative staff including the consortium coordinator, Dr. Janulewicz-Lloyd, and BU data coordinating center staff. The Administrative core will coordinate IRB protocol and regulatory submissions and approvals, data management and monitoring, statistical management of consortium data and perform research site performance evaluations. It will also establish a manual of operations for the clinical study protocols to ensure consistency across the three research recruitment sites. In addition, the administrative core will produce the required annual progress reports and updates and regulatory assurances. Financial management of the GWIC will also occur through the administrative core and will occur through subcontracts to each research site through the BU administrative core and grants financial management staff. Boston University is well equipped for administering the financial management of the GWIC because it has many other large multi-site studies that are centrally coordinated and financially managed through the school's office of sponsored programs and business office. Finally, the administrative core will provide coordination and ensure standardization of clinical studies within the consortium.

Task 3a. Quality control measures will be devised by administrative core to ensure robust data quality between study sites.

Data Management Service Group - The BUCC, in partnership with the Data Coordinating Center (DCC) at Boston University School of Public Health, will be responsible for data and statistical coordination for the Consortium (Figure 2). The Data Management Service Group will assist with quality control issues, data cleaning, management and data sharing as well as website management.

Investigators from the proposed BUCC have extensive experience in the management of sensitive research participant information and have been involved in large longitudinal cohort studies including The Ft. Devens

Cohort studies and the Framingham Heart Study (Drs. Sullivan, Krengel, Killiany and Heeren) as well as large multi-site national studies including VA Cooperative Study #458 National Health Survey of Gulf War Veterans and Their Families, the Vietnam Era Twin Study of Aging (Dr. Toomey), and the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Dr. Killiany). Collectively, the proposed BUCC personnel have extensive experience coordinating large longitudinal and multi-site studies including responsibility for reducing inter-rater drift and ensuring data reliability and secure data practices and quality control measures (Drs. Toomey and Krengel). These secure practices include using de-identified data with unique identifiers with keys to this coding system maintained in a secure location. The coded data are often entered into a password protected, secure, web-based system that protects the information provided at both the site level and the coordinating center level.

The DCC has been a data management resource center since 1984 and during this time has participated in hundreds of research projects including multi-center and international clinical trials. Responsibilities routinely include: design and creation of data collection protocols including case report forms and data dictionaries; subject and data tracking systems; training site personnel in data management and quality control procedures; site monitoring/auditing procedures; creation of coding manuals and Manuals of Operation; project web site design and management; design and implementation of a wide variety of data entry systems including web-based and scanning technology, with built-in range and verification capabilities; statistical analyses; and study closeout. The primary objective of the DCC will be to develop procedural consistency for the proposed consortium in order to ensure the highest data quality. This will be accomplished by the successful completion of the following tasks:

- **Design, construct and maintain secure consortium website.**
- **Design, construct and maintain a subject and specimen tracking systems.**
- **Provide and maintain a bar-coded specimen tracking system.**
- **Design standardized data collection forms.**

- **Provide Database Infrastructure**
- **Provide a Data Management Manual of Operations (MOP).**
- **Create analytic datasets for statistical programming**.

Statistical analysis - The statistical services working group will perform analyses and provide statistical planning and advice for study investigators. The DCC has 16 statistical analysts on its staff, with Masters-level training in Statistics, Biostatistics, Epidemiology, and/or Public Health. Analysts work closely with faculty members from the BU School of Public Health Department of Biostatistics to conduct statistical analyses on collaborative studies. Dr. Timothy Heeren, Professor of Biostatistics with 25 years of planning and performing statistical analyses for large research studies and teaching courses regarding biostatistical designs, will serve as the statistical director for the proposed BUCC. Under the direction of Dr. Heeren, the DCC Statistical Analyst will write the computer code for analyses (to be agreed upon by the DCC, Dr. Heeren and Study Investigators) for interim and final reports as well as for manuscripts, publications, and presentations.

Management and Communication Plan for GWI consortium - The GWIC will be coordinated by the Boston University Coordinating Center (BUCC) which will provide administrative support to the other research sites previously mentioned and will serve as the *Administrative Core* for the consortium. Central coordination for data management and data analyses will occur at the BUCC. As previously mentioned, the BU DCC has extensive experience with instituting and ensuring adequate quality control from multi-site studies. Research sites will be monitored for successful completion of study aims and for inter-rater reliability by planning quality control measures including duplicate samples sent for processing as well as other quality control measures. Research site performance will be monitored and tracked by having each investigator submit monthly project updates through the consortium web-based portal as well as through regular meetings of the Steering Committee. In this way, individual investigators will consistently share their ongoing study results to further develop and collectively identify pathobiological markers of GWI. To enhance

communication between the BUCC and individual research sites and collaborators, adobe connect pro web meeting software will continue to be employed that will allow virtual meetings to include white boards and slide presentations as well as Skype and iChat software utilization. In addition, an online Zotero group and Dropbox account will continue to be utilized to share publications and manuscript drafts for discussion and review. Working Groups will be implemented as well as quarterly meetings of all Steering Committee investigators. Working groups will include:

Table 4. GWIC Working Groups

Working Group	Tasks	Members
Data Management Service Group	Assist with QC issues, data cleaning and data management and sharing, website management.	Christine Chaisson, DCC Consortium PI, co-PIs
Statistics Service Group	Perform analyses and provides statistical planning and advice for study investigators and research site PIs.	Timothy Heeren, Christine Chaisson, Consortium PI and co-PIs
Translational Working Group	Forum for Intellectual property and material (IP) issues, translation of results into papers, abstracts, new grant submissions and how clinical and preclinical results can inform each other.	Michael Pratt – BU Tech Transfer office Consortium PI, co-PIs Research site PIs, RIO
Behavioral Studies Working Group	Plan imaging protocols and provide quality control for multiple imaging sites. Plan behavioral testing protocols and coordinate preclinical and clinical studies for comparability.	Drs. Sullivan, Killiany, Krengel, Toomey, Steele, Klimas, Coller, Hutchinson, Maier, Watkins
Histopathology Working Group	Plan tissue studies of proinflammatory, glial, axonal transport and mitochondrial markers in similarly dosed animal and cell models.	Drs. Baas, Black, O'Callaghan, Fields, Maier, Watkins
Immune Genetics Working Group	Plan and implement studies assessing brain-immune interactions involving glia and proinflammatory cytokines/chemokines through genetic SNPs and mRNA and miRNA protein studies.	Drs. Coller, Hutchinson, Klimas, Steele, Sullivan, Watkins, Maier

Task 3b. External Advisory Committee will be planned.

Oversight of the consortium will be coordinated by a Steering Committee that will be made up of the consortium PI, the individual research site PIs, BU Coordinating Center representatives and consumer advocates (GW veterans with GWI). The Steering Committee will finalize the consortium charter and by-laws and will monitor research site performance and determine individual study performance and

progress. The Steering Committee will also determine go/no-go procedure evaluations and amendments to the overall study plan and will provide for succession plans in the unlikely event that the consortium PI should leave Boston University. In this unlikely event, one of the capable and experienced co-PIs at BU could succeed Dr. Sullivan as consortium PI. An External Advisory Board (EAB) made up of the GWIRP integration panel, USAMRMC representatives and GWI researchers (not involved with the consortium) will provide oversight and guidance to the Grants Officer. The EAB chair and a representative of the USAMRMC will be invited to regularly scheduled steering committee meetings and will be provided agendas and meeting minutes from the planning meetings. In addition, the research site PIs will present written and oral briefings to the EAB and USAMRMC staff at semi-annual in-person meetings.

Task 4a. Identify potential intellectual property or materials that should be discussed among consortium collaborators.

The GWIC members met with Mr. Michael Pratt from the Boston University technology transfer office at our February 8, 2012 webinar meeting to devise a plan for any potential intellectual property (IP) or materials issues that might arise during the full consortium grant period. There were no clear IP issues identified during the planning discussion but a plan was devised to create a translational working group for the consortium in order to identify the best ways for the consortium to translate research results whether it is through presentations, journal articles, patents, obtaining further funding avenues or combinations thereof. Michael Pratt agreed to continue to advise the Translational Working Group and to act as a point of contact (POC) to resolve any potential intellectual property and material property issues among participating individuals and organizations.

Task 4b. Develop an intellectual property plan across all institutions and individuals.

An intellectual property plan was devised in consultation with Mr. Michael Pratt from the Boston University technology transfer office where all GWIC investigators were in agreement with the

approach to take regarding any potential intellectual property issues that may emerge during the consortium studies. The IP plan is as follows:

Intellectual Property Plan. This consortium will be aimed at identifying pathobiological mechanisms of Gulf War illness by using state of the art neuroimaging, genetic and blood biomarker studies that may identify viable treatment avenues for ill Gulf War veterans.

There are no known patents or patentable deliverables thought to result from the work of the consortium however, all consortium collaborators will have specific tasks identified in the grant proposal and will plan to share in publications that may come from the full consortium. Several of the consortium members have a track record of prior collaboration and shared publications and will continue to work together in a collaborative fashion for this consortium study.

The state of the art PET imaging will use newly created ligands devised by RIO pharmaceuticals. The excitatory amino acid transporter target (EAAT2) Positron Emission Tomography (PET) imaging radiotracer is protected with intellectual property held by Rio Pharmaceuticals. Provisional and full patent applications have been filed (2007-2010). The applications are advancing through their respective established patent granting processes. Rio Pharmaceuticals has secured the intellectual property rights and possesses clear freedom to operate across these domains. As a key part of RIO's business strategy, RIO will provide these new, highly selective PET ligands to the consortium in order to identify specific types of neurotransmitter systems altered in Gulf War Illness.

A Translational Working Group will be established in order to identify the best ways for the consortium to translate research results whether it is through presentations, journal articles, patents, obtaining further funding avenues or combinations thereof. Mr. Michael Pratt from the Boston University Technology Transfer office has consulted with the GWIC members regarding devising an

intellectual property and materials plan and will continue to advise the Translational Working Group and to act as a point of contact (POC) to resolve any potential intellectual property and material property issues among participating individuals and organizations. The translational working group will be comprised of a member from each participating organization in the consortium and will meet twice annually to review research progress, review new discoveries and potential invention disclosures, discuss opportunities for practical application, and agree how the consortium will support translation of those discoveries to maximize the benefit for treatment and understanding of GWI.

Task 5a. Finalize GWIC consortium plan regarding specific study aims and scientific collaborators.

During the two in-person and monthly webinar meetings of the GWI consortium, the GWIC consortium plan regarding the specific study aims and scientific collaborations were agreed upon by all GWIC investigators and finalized in order to submit the full GWIC consortium grant to CDMRP in June 2012 for review. The full consortium proposal was recommended for funding in October 2012.

Task 5b. Write brief final planning summary report documenting GWIC plans for Consortium Cores and to Identify Research Sites for Planned Studies.

This report provides a planning summary report documenting the GWIC plans for administrative, preclinical and clinical consortium cores and the nine research sites that have been chosen for our planned studies in the GWI consortium grant that was submitted to CDMRP Gulf War Illness Research Program on June 19, 2012 for review and was recommended for funding in October, 2012.

Task 5c. Prepare GWIC Consortium grant draft for submission.

The Brain-Immune Interactions as the Basis of Gulf War Illness: Gulf War Illness Consortium (GWIC) grant application was prepared by the GWIC members and submitted by Dr. Sullivan at the Boston University Medical Campus for review by the CDMRP Gulf War Illness Research Program on June 19, 2012. Dr. Sullivan was notified that the GWIC consortium application was recommended for funding on October 16, 2012.

KEY RESEARCH ACCOMPLISHMENTS

- New collaborations were established among highly productive investigators from several interdisciplinary fields including neurotoxicology, neuropsychology, neuroimaging, neuroinflammation, immunology, genetics and cell biology.
- New collaborations were established among research investigators from government and non-government agencies.
- A successful strategy for monthly in-person or web-based meetings was established with this international research team.
- A highly integrative and testable theory of Gulf War Illness was developed as part of a consortium grant application that was submitted for review.
- A highly structured consortium was developed that includes Administrative, Preclinical and Clinical Research Cores.
- Working groups and a Steering Committee were designed to maximize collaborative efforts and to reduce redundancy of resources.
- A Translational Working Group was designed to identify the best ways for translation of research results.
- A web site was designed for consortium investigators to share and edit grant sections, and to review prior meeting minutes.

REPORTABLE OUTCOMES:

Publications – * relevant publications to the theoretical development of GWIC hypotheses and specific aims are highlighted.

Peter Baas

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Mark Black

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Janet Coller

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protects mice from acute alcohol-induced sedation and/or motor impairment. *Brain, Behavior, and Immunity* 25 Suppl 1: S155-S164.

Douglas Fields

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Invited Presentations

1. Sullivan, K. The BUSPH Gulf War Illness Research Program: An Overview, Environmental Health Department Research Retreat, Boston University School of Public Health, November 17, 2012.

2. Steele, L. 21 years after Desert Storm: What have we learned about the health of Gulf War Veterans? Palo Alto VA Continuing Education Conference Gulf War Illnesses: What Providers Should Know. Palo Alto, CA, July 12, 2012.

3. Sullivan, K. Neurotoxicity of Gulf War Deployment: The Neuropsychological and Neuroimaging Correlates. Palo Alto VA Continuing Education Conference Gulf War Illnesses: What Providers Should Know. Palo Alto, CA, July 12, 2012.

4. Klimas, N. From Bedside to Bench and Back Again: Untangling the Mystery of Gulf War Illness. Palo Alto VA Continuing Education Conference Gulf War Illnesses: What Providers Should Know. Palo Alto, CA, July 12, 2012.

5. Sullivan, K., Krengel, M. Structural MRI and Cognitive Correlates in Military Pest Control Personnel. Research Advisory Committee on Gulf War Veterans Illnesses meeting, Boston, MA, June 19, 2012.

6. Krengel, M., Janulewicz, P., Chamberlian, J., Yuan, J., Valmas, M & **Sullivan, K.** Gulf War Illness: A meta-analytic review of cognitive findings. International Neuropsychological Society, 40th Annual Meeting, Montreal, Canada, February 2012 (Poster Presentation).

7. Sullivan, K**.** Chronic Health Effects of Pesticide Exposure in Military Pesticide Applicators. Gijs Van Seventer Doctoral Seminar, Boston University School of Public Health, October, 2011.

PIs manuscripts in preparation: (from previous DOD funding sources)

1. Sullivan, Krengel et al., Neuropsychological Functioning in Military Pesticide Applicators from Gulf War I: Effects on Information Processing Speed and Visual Memory.
2. Sullivan, Krengel et al., Health Symptom Patterns in pesticide applicators from Gulf War I.
3. Krengel, Sullivan et al., A Meta-Analysis of Cognitive Functioning in Gulf War Veterans.
4. Sullivan, Krengel et al. A Meta-analysis of Health Symptom Report in Gulf War Veterans.

Relevant Funding:

1. Drs. Sullivan and Krengel submitted two recent grants (August 2010 / August 2011) to the congressionally directed medical research program (CDMRP) to study the chronic health symptom trajectories in GW veterans from the Ft. Devens Cohort and to begin a novel treatment for GW illness by using intranasal insulin in collaboration with researchers from the Bronx VA. Both grants were recommended for funding and have both begun.

2. Dr. Sullivan and this highly collaborative team of researchers from ten study sites around the country and Australia submitted a Gulf War Illness Consortium grant on June 19, 2012 entitled, Brain-Immune Interactions as the Basis of Gulf War Illness: Gulf War Illness

Consortium (GWIC) to the CDMRP for review and this grant was recommended for funding on October 16, 2012. A pre-award meeting with CDMRP has been planned.

CONCLUSIONS:

This multi-institutional collaboration of highly qualified GWI researchers from public universities, federal agencies, and the private sector, provide an unprecedented opportunity to more fully elucidate the underlying pathobiology of Gulf War illness in one integrated model that once proven, will lead to focused treatment trials that can be quickly implemented.

The central hypothesis for the pathobiological mechanisms of GWI in this consortium includes chronic neuroinflammation as a result of initial glial *activation* and then *priming* of glial responses that cause stronger and longer responses that do not shut off the chemical cascade of proinflammatory cytokines and chemokines that cross-talk between the immune system and the brain. This could result in a lasting multisystem illness affecting many body systems, as seen in GWI.

Improved understanding of the role of glial activation in chronic pain states has given rise to rapidly expanding efforts to identify pharmaceuticals that specifically focus on glial functions. The growing availability of treatments of this type gives particular urgency to our efforts to determine the extent to which glial activation and central cytokine activation explain the symptoms of GWI. In order to specifically address the research gaps outlined by the IOM and the RAC reports with regard to biomarker identification and pathobiology of GWI, this research team will be characterizing disease symptoms and validating and improving pathobiological markers based on collective prior clinical and preclinical studies and leveraging longitudinal cohorts and stored blood samples with the ultimate goal of identifying targeted and effective treatments for GWI.

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medical, and other substance use confounds. We conducted a linear regression with IGT net score and amount of cannabis use as independent variables – MPS score was the dependent variable. Three regressions were conducted, with each having a different parameter of cannabis use (i.e., cannabis use in the last 30 days, last 12 months, and lifetime).
Results: Significant IGT x cannabis use interactions were significant for the last 30 days and 12 months (p-values = .04), and suggested a trend toward significance with lifetime use (p = .06). Follow-up tests of the interactions revealed that across all models, greater amounts of cannabis use were associated with higher MPS scores among participants with lower IGT scores (p-values = .003 to .02; R2 = .17 to .30), but not among those with better performance (p-values > .63). This was not accounted for by differences in amounts of cannabis use or MPS scores between better and poorer performers on the IGT (all p-values > .26).
Conclusions: DM was found to influence the relationship between amount of cannabis use and the negative consequences experienced by users. Amount of cannabis did not affect the number of consequences reported by those with better DM. In contrast, those with poorer DM experienced more negative consequences with more cannabis use. It may be that those with better DM are better able to inhibit their cannabis use in situations where it may lead to negative consequences. Supported by K23DA023560 to RG.
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R. GONZALEZ, R.M. SCHUSTER, N. CRANE, E.M. MARTIN & J. VASSILEVA. Decision-Making Influences the Relationship between Cannabis Harm Perception and Negative Consequences Reported from its Use: Preliminary Findings.
Objective: Addiction is often defined as compulsive use of a substance despite experiencing repeated negative consequences from its use, and has been associated with deficits in decision-making (DM). General perceptions of a drug's harm may influence its use and the magnitude of personal negative consequences reported. Here, we examine this hypothesized relationship and how it may be influenced by DM.
Participants and Methods: Participants were 54 young adults who identified cannabis as their drug of choice, used cannabis in the last 30 days, and were free of important medical, mental health, and other substance use confounds. They completed the Iowa Gambling Task (IGT; a measure of decision-making) and the Marijuana Problems Scale (MPS; a self-report questionnaire on problems experienced from cannabis use in the last 90 days). Perceptions of harm from cannabis use were assessed with the Cannabis Harm Perception (CHP) questionnaire: a self-report measure being developed to assess negative perceptions of cannabis use.
Results: Linear regression with IGT and CHP as IVs and scores on the MPS as the DV revealed a significant interaction (p < .01). Greater perceived harm on the CHP was associated with more cannabis problems on the MPS, but only among those with poorer DM (R2 = .57, p < .0001). No significant relationships emerged between CHP and MPS among those with better DM (R2 = .01, p = .59).
Conclusions: Our preliminary findings are the first to examine and report that DM influences the relationship between general perceptions of harm from cannabis use and the degree to which an individual endorses negative consequences. Those with better DM may have more accurate self-assessments of the negative events they experience from cannabis use and may be less influenced by their general perceptions of cannabis' harmful effects. For those with poorer DM, the negative events they report from cannabis appear to be strongly influenced by their general perceptions of cannabis' harmful effects. Supported by K23DA023560 to RG.
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M. KRENGEL, P. JANULEWICZ, J. CHAMBERLAIN, J. YUAN, M. VALMAS & K. SULLIVAN. Gulf war illness: A meta-analytic review of cognitive findings.
Objective: Gulf war veterans continue to suffer from chronic multisystem illness, including cognitive concerns. Several research studies on cognitive correlates have been conducted since the end of the Gulf War and researchers have often but not consistently found diminishment in areas of short-term memory, attention, motor speed and mood, relative to non-deployed era veterans and norms. When examining potential causative factors such as neurotoxicant exposures, highly exposed groups have been found to be more impaired relative to minimally exposed. It was the purpose of the current study to critically review the literature on the neuropsychological deficits in GW Ill veterans and conduct a meta-analysis to more adequately describe the cognitive correlates of GW-deployment.
Participants and Methods: Twenty-seven studies met inclusion criteria. Each study was reviewed methodologically by 2 trained raters using a systematized critique form adapted for this study. Dependent variables were classified based on cognitive domain and data were analyzed in relationship to relevant predictor variables. Analyses from each paper were entered into a large database and the average effect sizes computed by domain listed above.
Results: Overall analyses were compared for GW ill and non-ill veterans and showed more discriminating results than GW deployed versus era veterans. Exposure variables also showed different effect sizes in the cognitive domains of interest.
Conclusions: By systematically reviewing the literature on GW illness and cognitive correlates and determining the average effect size per cognitive domain, it is possible to determine the extent to which cognitive impairment occurs in this population. Similar meta-analytic reviews would help to clarify equivocal results in health symptoms and neuroimaging findings in this population.
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S. LEBLANC-MENZIES, J.G. KEILP, A.K. BURKE, M.A. OQUENDO & J.J. MANN. Smoking in Depression: Associations with Cognition and Cognitive Risk Factors for Suicide Attempt.
Objective: Cigarette smoking is associated with a variety of deficits in cognitive performance, encompassing psychomotor, memory, and executive functions. In major depression, smoking is a risk factor for suicidal behavior. Smoking in depressed patients may be related to more severe cognitive impairment, and possibly to cognitive deficits associated with suicide attempt risk.
Participants and Methods: 95 participants with current major depression and a reported history of smoking, 176 depressed non-smokers, and 63 non-smoking non-patient volunteers were administered a battery of neurocognitive tests assessing motor speed, psychomotor performance, attention, memory, abstraction, working memory, language fluency, and impulse control.
Results: Smokers performed more poorly than all other groups on speeded measures, including Choice Reaction Time (p=.004), WAIS Digit Symbol (p=.001), A Not B Timed Reasoning (p=.01), and Category Fluency (p=.002), but also on WAIS Vocabulary (p=.01), an estimate of intelligence. Controlling for Vocabulary, differences in A Not B and Category Fluency became marginally non-significant. Smoking was not related to performance on measures that consistently discriminate past suicide attempters, including a computerized Stroop task and Buschke Selective Reminding Test (Keilp et al., 2001; Keilp et al., in press).
Conclusions: Depressed smokers were slowed in terms of reaction time, processing speed, and semantic fluency relative to depressed non-smokers. It is unclear if this is a direct result of nicotine exposure, or a compensation for more severe slowing in the context of their depression. Smoking was not related to other cognitive impairments that discriminate suicide attempters, suggesting that its contributions to risk are independent of neurocognition.